

CLAIMS

What is claimed is:

1. A method of assessing relative susceptibility of a human to oxidative damage, the method comprising assessing occurrence in the human's genome of disorder-associated polymorphisms in at least two genes selected from the group consisting of
 - a) genes which encode an enzyme that catalyzes conversion of a toxic oxygen species to a less toxic oxygen species;
 - b) genes which encode a protein that provides protection against oxidative stress;
 - 10 c) genes which encode a protein that induces production of a toxic oxygen species;
 - d) genes which encode a protein that indirectly affects oxidative stress; and
 - e) genes which encode a protein for which the level of expression of the protein is associated with oxidative stress,
- 15 whereby occurrence of any of the polymorphisms is an indication that the human is more susceptible to oxidative damage than a human whose genome does not comprise the polymorphism, and whereby occurrence of a plurality of the polymorphisms is an indication that the human is even more susceptible to oxidative damage than a human whose genome does not comprise the polymorphisms.
- 20
2. The method of claim 1, wherein the genes are selected from the group consisting of a), b), c), and d).
3. The method of claim 1, wherein the genes are selected from the group
- 25 consisting of a), b), and c).
4. The method of claim 1, comprising assessing occurrence in the human's genome of disorder-associated polymorphisms in at least four genes selected from the group consisting of genes which encode an enzyme that catalyzes conversion of a toxic oxygen
- 30 species to a less toxic oxygen species.

5. The method of claim 4, wherein the genes are

- i) the gene which encodes mitochondrial manganese superoxide dismutase (MnSOD),
- ii) the gene which encodes cytoplasmic copper/zinc superoxide dismutase (CZSOD),
- iii) the gene which encodes catalase, and
- iv) the gene which encodes glutathione peroxidase.

6. The method of claim 1, wherein the genes are selected from the group

consisting of

- i) the gene which encodes MnSOD,
- ii) the gene which encodes CZSOD,
- iii) the gene which encodes catalase,
- iv) the gene which encodes glutathione peroxidase,
- v) the gene which encodes glutathione S-transferase,
- vi) the gene which encodes glutathione reductase,
- vii) the gene which encodes thioredoxin reductase,
- viii) the gene which encodes paraoxonase,
- ix) the gene which encodes NAD(P)H:quinone oxidoreductase 1,
- x) the gene which encodes 8-oxo-7,8-dihydrodeoxyguanosine triphosphatase,
- xi) the gene which encodes epoxide hydrolase,
- xii) the gene which encodes myeloperoxidase,
- xiii) the gene which encodes tumor necrosis factor alpha,
- xiv) the gene which encodes NADH/NADPH oxidase p22 phox protein,
- xv) the gene which encodes nitric oxide synthase
- xvi) the gene which encodes xanthine oxidase,
- xvii) the gene which encodes cytochrome P450,
- xviii) the gene which encodes apolipoprotein E,
- xix) the gene which encodes UDP-glucuronosyltransferase 1A1,
- xx) the gene which encodes acid phosphatase,
- xxi) the gene which encodes protein phosphotyrosine phosphatase,

- xxii) the gene which encodes epinephrine oxidase,
- xxiii) the gene which encodes cystathionine beta-synthase,
- xxiv) the gene which encodes cystathionine gamma-lyase,
- xxv) the gene which encodes N5-methyl THF:homocysteine methyltransferase,
- 5 xxvi) genes which encode an S-adenosylmethionine methyltransferase, and
- xxvii) genes which encode a heat shock protein.

7. The method of claim 6, the genes are selected from the group consisting of i) through iv).

8. The method of claim 6, the genes are selected from the group consisting of i) through xi).

9. The method of claim 6, the genes are selected from the group consisting of i) through xvii).

10. The method of claim 6, comprising assessing occurrence in the human's genome of disorder-associated polymorphisms in at least four of i) through xxvii).

11. The method of claim 6, comprising assessing occurrence in the human's genome of disorder-associated polymorphisms in at least six of i) through xxvii).

12. The method of claim 6, comprising assessing occurrence in the human's genome of disorder-associated polymorphisms in at least ten of i) through xxvii).

13. The method of claim 6, comprising assessing occurrence in the human's genome of disorder-associated polymorphisms in at least fifteen of i) through xxvii).

14. The method of claim 1, wherein occurrence of an individual disorder-associated polymorphism is assessed by

contacting a nucleic acid derived from the human's genome with a first
oligonucleotide that anneals with higher stringency with the disorder-associated
polymorphism than with a corresponding non-disorder-associated polymorphism and
assessing annealing of the first oligonucleotide and the nucleic acid,

5 whereby annealing of the first oligonucleotide and the nucleic acid is an indication
that the human's genome comprises the disorder-associated polymorphism.

10 15. The method of claim 14, wherein the first oligonucleotide is attached to
a support.

16. The method of claim 15, wherein the support has a plurality of different
first oligonucleotides attached thereto.

15 17. The method of claim 16, wherein the support has attached thereto at least
five first oligonucleotides that anneal with higher stringency with the disorder-associated
polymorphisms than with the corresponding non-disorder-associated polymorphisms.

20 18. The method of claim 16, wherein the support has attached thereto at least
ten first oligonucleotides that anneal with higher stringency with the disorder-associated
polymorphisms than with the corresponding non-disorder-associated polymorphisms.

25 19. The method of claim 16, wherein the support has attached thereto at least
fifteen first oligonucleotides that anneal with higher stringency with the disorder-associated
polymorphisms than with the corresponding non-disorder-associated polymorphisms.

20. The method of claim 14, wherein the first oligonucleotide is a molecular
beacon oligonucleotide.

30 21. The method of claim 14, wherein occurrence of an individual disorder-
associated polymorphism is further assessed by

contacting the nucleic acid with a second oligonucleotide that anneals with higher stringency with a non-disorder-associated polymorphism than with the corresponding non-disorder-associated polymorphism and

assessing annealing of the second oligonucleotide and the nucleic acid,

5 whereby annealing of the second oligonucleotide and the nucleic acid is an indication that the human's genome does not comprise the disorder-associated polymorphism.

10 22. The method of claim 21, wherein the second oligonucleotide is attached to a support.

23. The method of claim 22, wherein the first and second oligonucleotides are attached to the same support.

15 24. The method of claim 21, wherein the second oligonucleotide is a molecular beacon oligonucleotide.

20 25. The method of claim 24, wherein the first and second oligonucleotides are spectrally distinct molecular beacon oligonucleotides.

26. The method of claim 1, further comprising calculating a susceptibility score by summing, for each of the selected genes in which a disorder-associated polymorphism occurs in the human's genome, the product of a constant and a correlation factor, wherein the correlation factor represents the fraction of humans heterozygous or
25 homozygous for the disorder-associated polymorphism who exhibit the corresponding disorder, whereby the susceptibility score represents the relative susceptibility of the human to oxidative damage.

30 27. The method of claim 26, wherein the same constant is used for each selected gene.

28. The method of claim 26, wherein the constant used for each gene of group a) is greater than the constant used for the genes of groups b), c), d), and e).

29. The method of claim 28, wherein the constant used for each gene of group a) is at least twice as great as the constant used for the genes of groups b), c), d), and e).

30. The method of claim 29, wherein the genes are selected from the group consisting of a), b), and c).

31. The method of claim 30, wherein the genes are selected from the group consisting of

- i) the gene which encodes MnSOD,
- ii) the gene which encodes CZSOD,
- iii) the gene which encodes catalase,
- iv) the gene which encodes glutathione peroxidase,
- v) the gene which encodes glutathione S-transferase,
- vi) the gene which encodes glutathione reductase,
- vii) the gene which encodes thioredoxin reductase,
- viii) the gene which encodes paraoxonase,
- ix) the gene which encodes NAD(P)H:quinone oxidoreductase 1,
- x) the gene which encodes 8-oxo-7,8-dihydrodeoxyguanosine triphosphatase,
- xi) the gene which encodes epoxide hydrolase,
- xii) the gene which encodes myeloperoxidase,
- xiii) the gene which encodes tumor necrosis factor alpha,
- xiv) the gene which encodes NADH/NADPH oxidase p22 phox protein,
- xv) the gene which encodes nitric oxide synthase
- xvi) the gene which encodes xanthine oxidase, and
- xvii) the gene which encodes cytochrome P450.

32. The method of claim 31, comprising assessing occurrence in the human's genome of disorder-associated polymorphisms in at least four of i) through xvii).

33. The method of claim 31, comprising assessing occurrence in the human's genome of disorder-associated polymorphisms in at least six of i) through xvii).

34. The method of claim 31, comprising assessing occurrence in the human's genome of disorder-associated polymorphisms in at least ten of i) through xvii).

35. The method of claim 31, comprising assessing occurrence in the human's genome of disorder-associated polymorphisms in at least fifteen of i) through xvii).

36. The method of claim 1, wherein each of the polymorphisms is a single nucleotide polymorphism (SNP).

37. The method of claim 36, wherein occurrence of a SNP is assessed by annealing a nucleic acid derived from the human's genome with a primer that is complementary to the region adjacent the SNP on its 3' side, extending the primer using a polymerase in order to add a nucleotide residue complementary to the SNP to the primer, and detecting the identity of the nucleotide residue complementary to the SNP.

38. The method of claim 37, wherein the nucleotide residue is a non-extendable residue.

39. A method of selecting a dose of an anti-oxidant composition for administration to a human, the method comprising assessing occurrence in the human's genome of disorder-associated polymorphisms in at least one gene selected from the group consisting of

a) genes which encode an enzyme that catalyzes conversion of a toxic oxygen species to a less toxic oxygen species;

- b) genes which encode a protein that provides protection against oxidative stress;
- c) genes which encode a protein that induces production of a toxic oxygen species;
- 5 d) genes which encode a protein that indirectly affects oxidative stress; and
- e) genes which encode a protein for which the level of expression of the protein is associated with oxidative stress,

whereby occurrence of any of the polymorphisms is an indication that a greater dose of the composition should be administered to the human; and

10 selecting a dose of the composition based on occurrence of the polymorphisms.

40. A kit for assessing relative susceptibility of a human to oxidative damage, the kit comprising reagents for assessing occurrence in the human's genome of disorder-associated polymorphisms in at least two genes selected from the group consisting
15 of

- a) genes which encode an enzyme that catalyzes conversion of a toxic oxygen species to a less toxic oxygen species;
- b) genes which encode a protein that provides protection against oxidative stress;
- 20 c) genes which encode a protein that induces production of a toxic oxygen species;
- d) genes which encode a protein that indirectly affects oxidative stress; and
- e) genes which encode a protein for which the level of expression of the protein is associated with oxidative stress.

25

41. The kit of claim 40, wherein the reagents comprise first oligonucleotides that anneal with higher stringency with the disorder-associated polymorphisms than with corresponding non-disorder-associated polymorphisms.

30

42. The kit of claim 41, wherein each of the first oligonucleotides is attached to a support.

43. The kit of claim 42, wherein each of the first oligonucleotides is attached to the same support.

5 44. The kit of claim 42, wherein each of the first oligonucleotides is attached to a different support.

45. The kit of claim 41, wherein the first oligonucleotides are molecular beacon oligonucleotides.

10

46. The kit of claim 41, wherein the kit further comprises second oligonucleotides that anneal with higher stringency with the non-disorder-associated polymorphisms than with corresponding disorder-associated polymorphisms.

15

47. The kit of claim 46, wherein the first and second oligonucleotides are spectrally distinct molecular beacon oligonucleotide pairs.

48. The kit of claim 40, wherein the reagents comprise primers that are complementary to the region adjacent a characteristic residue of the disorder-associated polymorphism for amplifying at least the characteristic residue.

20

49. The kit of claim 48, further comprising a polymerase capable of extending the primers by adding a nucleotide residue complementary to the characteristic residue.

25

50. The kit of claim 49, further comprising a non-extendable nucleotide residue.

51. The kit of claim 40, further comprising an instructional material which includes a numerical value representing the product of a constant and a correlation factor, wherein the correlation factor represents the fraction of humans heterozygous or

30

homozygous for the disorder-associated polymorphism who exhibit the corresponding disorder.

5 52. The kit of claim 51, wherein the same constant is used for each selected gene.

53. The kit of claim 51, wherein the constant used for each gene of group a) is greater than the constant used for the genes of groups b), c), d), and e).

10 54. The kit of claim 51, wherein the constant used for each gene of group a) is at least twice as great as the constant used for the genes of groups b), c), d), and e).

15 55. The kit of claim 40, wherein the genes are selected from the group consisting of a), b), and c).

56. The kit of claim 40, wherein the genes are selected from the group consisting of

- i) the gene which encodes MnSOD,
- ii) the gene which encodes CZSOD,
- 20 iii) the gene which encodes catalase,
- iv) the gene which encodes glutathione peroxidase,
- v) the gene which encodes glutathione S-transferase,
- vi) the gene which encodes glutathione reductase,
- vii) the gene which encodes thioredoxin reductase,
- 25 viii) the gene which encodes paraoxonase,
- ix) the gene which encodes NAD(P)H:quinone oxidoreductase 1,
- x) the gene which encodes 8-oxo-7,8-dihydrodeoxyguanosine triphosphatase,
- xi) the gene which encodes epoxide hydrolase,
- xii) the gene which encodes myeloperoxidase,
- 30 xiii) the gene which encodes tumor necrosis factor alpha,
- xiv) the gene which encodes NADH/NADPH oxidase p22 phox protein,

- xv) the gene which encodes nitric oxide synthase
- xvi) the gene which encodes xanthine oxidase,
- xvii) the gene which encodes cytochrome P450,
- xviii) the gene which encodes apolipoprotein E,
- 5 xix) the gene which encodes UDP-glucuronosyltransferase 1A1,
- xx) the gene which encodes acid phosphatase,
- xxi) the gene which encodes protein phosphotyrosine phosphatase,
- xxii) the gene which encodes epinephrine oxidase,
- xxiii) the gene which encodes cystathionine beta-synthase,
- 10 xxiv) the gene which encodes cystathionine gamma-lyase,
- xxv) the gene which encodes N5-methyl THF:homocysteine methyltransferase,
- xxvi) genes which encode an S-adenosylmethionine methyltransferase, and
- xxvii) genes which encode a heat shock protein.

- 15 57. The kit of claim 56, wherein the genes are selected from the group consisting of i) through xvii).